aminergic and noradrenergic neurones (9).

An interaction between cholinergic and dopaminergic neurotransmitter systems has been postulated as the mechanism of neuroleptic catalepsy (24). Dopaminergic inputs on striatal cholinergic neurones and cholinergic inhibitory effects on striatal dopaminergic cell bodies have been established (25). A similar inverse relationship between striatal serotonergic and dopaminergic systems has been envisaged (25) in neuroleptic catalepsy (15). It is likely that PGE_1 exerts its cataleptic effect by modulating serotonergic, cholinergic and dopaminergic neurotransmission. Increased cholinergic and serotonergic activity, concomitant with reduced dopaminergic activity of rat brain, is reflected in the cataleptic state induced by PGE_1. The ability of $PGF_{2\alpha}$ to inhibit PGE_1 catalepsy lends credence to the hypothesis that the two PGs function in opposite directions in modulating rat brain serotonergic activity (8). The inability of diclofenac, a PG synthesis inhibitor, to affect PGE_1 catalepsy, is entirely predictable since the PG was administered exogenously.

An interesting aspect revealed in the present study relates to the inhibitory effect of naloxone on PGE_1 catalepsy. Little information exists on the possible inter-relationships between PGs and the endogenous opioid peptides, apart from isolated reports (22). Since both these groups of neuroregulators have been envisaged to act as modulators of central neurotransmission, such studies are necessary for better understanding of the complexities of synaptic transmission in the central nervous system.

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Morphine Inhibition of Theophylline Clearance

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Abstract: The effects of morphine on the single dose pharmacokinetics of theophylline were examined in two groups (6 rats/group) of male Sprague-Dawley rats after the administration of theophylline (6.25 mg/kg) alone and in conjunction with a 5 mg /kg I.V. dose of morphine sulfate. Concomitant morphine administration resulted in a 55 % reduction in theophylline clearance (0.14 ± 0.04 vs. $0.31 \pm 0.061 \cdot h^{-1} kg^{-1}$; $p < 0.0005$). The reduction in theophylline clearance with morphine administration was accompanied by a significant prolongation in theophylline half-life (3.5 ± 1.5 vs. 1.4 ± 0.35 h; $p < 0.02$). No changes in the volume of distribution of theophylline occurred with co-administration of morphine. The mechanism of this pharmacokinetic interaction may be partially related to competition between theophylline and morphine for enzymes which metabolize these compounds.

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Intravenous morphine and aminophylline have been widely used together in the treatment of acute pulmonary edema. Piafsky et al. (1) have examined the disposition of theophylline in nine patients with acute cardiogenic pulmonary edema (five of whom received morphine) and have noted a 33 % decrease in the systemic clearance of theophylline. Potential causes for this reduced clearance of theophylline include hypoxemia, hepatic congestion, or a drug interaction between theophylline and other drugs which were co-administered.

The existence of a common metabolic pathway for both morphine and theophylline suggests the potential for a drug-drug interaction. Both of these drugs are partially metabolized by *N*-demethylation pathways in the liver. Competition of morphine and theophylline for drug metabolizing enzymes

could contribute to the decrease in the clearance of theophylline noted. To our knowledge, no evaluation of this interaction has been made to date.

The purpose of the present study was to examine the effect of intravenous morphine on theophylline disposition in the rat.

Methods

Animal Dosing

Twelve male Sprague-Dawley rats (250 to 300 g; Perfection Breeders Inc., Douglassville, PA) were randomly assigned to two treatment groups (6 rats/group). Rats were lightly anesthetized with diethylether prior to insertion of a catheter for blood sampling. Once anesthetized, silastic tubing (0.02″ ID, Dow Corning, Midland, MI) was inserted into the right atrium via the right jugular vein. Drug(s) were injected into the left jugular vein at least 45 min following anaesthesia. All rats were alert at the time of dosing. Each rat in group 1 received a 5 mg/kg intravenous dose of morphine sulfate (4.25 mg/kg morphine equivalent dose) and a 6.25 mg/kg intravenous dose of theophylline within 5 min of each other. Blood samples (0.4 ml) were obtained prior to drug administration, and at 0.08, 0.17, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0 and 7.0 h after drug administration. Blood was collected into polypropylene bullets and centrifuged. Serum was harvested and stored at −20° until analysis. Each rat in group 2 received a 6.25 mg/kg intravenous dose of theophylline alone, with blood samples obtained at the same times as those in group 1. Serum samples were analyzed for theophylline by a modification of the high performance liquid chromatographic technique of Adams et al. (2). This assay was linear over the entire concentration range (0 to 20 μg/ml). The assay sensitivity was 0.1 μg/ml and the coefficients of variation for the low (2.7 μg/ml), medium(5.9 μg/ml) and high (16.5 μg/ml) quality control standards were 6.6, 3.7 and 3.0%, respectively. Morphine did not interfere with the quantitation of theophylline by this method.

Pharmacokinetic Analysis

Theophylline plasma concentration-time data from individual rats were analyzed by the LAGRAN computer program which performs area and moment analysis of plasma concentration-time data (3).

The systemic clearance of theophylline (CL) was computed using Eq. 1:

$$CL = \frac{Dose}{AUC} \qquad \text{(Eq. 1)}$$

where Dose is the theophylline dose administered and AUC is the total area under the plasma concentration-time curve.

The volume of distribution at steady-state of theophylline (V_{ss}) was computed using (Eq. 2):

$$V_{ss} = \frac{Dose \cdot AUTC}{(AUC)^2} \qquad \text{(Eq. 2)}$$

where AUTC is the first moment of the theophylline plasma concentration-time curve (4). The theophylline elimination rate constant (λ_Z) was determined from the slope of the least squares regression line of a log-linear plot of plasma concentrations versus time for all points in the elimination phase of theophylline disposition.

Theophylline plasma half-life ($t_{1/2}$) was computed with the equation $t_{1/2} = \ln(2)/\lambda_Z$.

Results

The mean (± SD) theophylline serum concentration-time plots when administered alone and in combination with morphine are presented in Fig. 1. Serum concentrations of theophylline declined in a first-order fashion with time whether administered alone or in combination with morphine. A dramatic reduction in the mean elimination rate constant λ_Z (± SD) (h^{-1}) for theophylline in the presence of morphine occurred [0.24(0.11) vs. 0.54 (0.12); $p <$ 0.002)]. The systemic clearance values of theophylline ($l \cdot h^{-1}\ kg^{-1}$) when administered alone and with morphine are plotted for each rat in Fig. 2. The mean clearance (± SD) of theophylline when administered concomitantly with morphine was substantially reduced when compared to control values [0.14(0.04) vs. 0.31(0.06); $p < 0.0005$]. The serum half-life of theophylline for the individual rats in each of the groups is presented in Fig. 3. The serum half-lives of theophylline when co-administered with morphine were significantly longer than

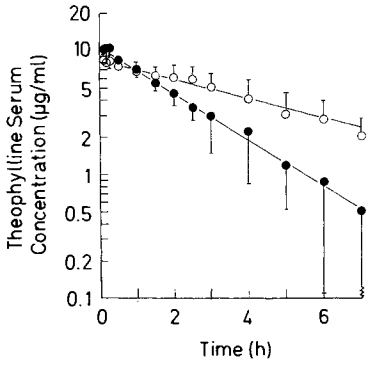

Fig. 1 Mean (± SD) serum concentrations of theophylline following a 6.25 mg/kg intravenous dose of theophylline alone (●; n=6) and in conjunction with a 5 mg/kg intravenous dose of morphine sulfate (○; n=6).

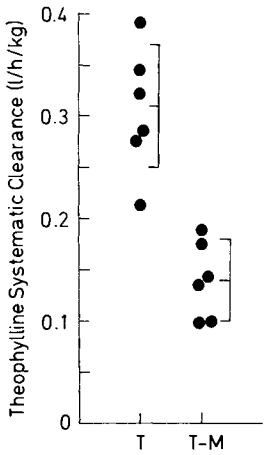

Fig. 2 Theophylline systemic clearance ($l \cdot h^{-1}\ kg^{-1}$) in rats receiving theophylline alone (T) and in conjunction with morphine (T-M). Each point represents the systemic clearance value from an individual rat. The solid lines indicate the mean (± SD) for each group. A significant difference in the clearance between the two groups was observed ($p < 0.0005$).

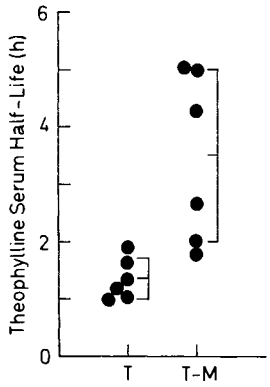

Fig. 3 Theophylline half-life (h) in rats receiving theophylline alone (T) and in conjunction with morphine (T-M). Each point represents the half-life value from an individual rat. The solid lines indicate the mean (± SD) for each group. A significant difference in the half-life between the two groups was observed ($p < 0.02$).

those obtained in the control rats [3.5 (1.5) vs. 1.4(0.35) h; $p < 0.02$]. The mean theophylline V_{ss} ($\pm$ SD) in the rats receiving morphine was not significantly different from control values [0.64(0.14) vs. 0.65(0.13) l/kg; N.S.].

Discussion

The reduced clearance of theophylline resulting with co-administration of morphine indicates that morphine affects theophylline metabolism either by a direct competition for drug metabolizing enzymes or by effects on some other physiologic processes which may modulate theophylline disposition. This reduction in the systemic clearance produced a substantial prolongation in the half-life of theophylline in the rats which received concomitant morphine.

Theophylline disposition in the rat is characterized by metabolism to at least two metabolites, 1,3-dimethyluric acid and 1-methylxanthine. Evidence suggests that this metabolism occurs through cytochrome P-450 and P-448 mediated pathways (5). Further biotransformation of 1-methylxanthine to 1-methyluric acid by xanthine oxidase also occurs. Lohmann et al. (5) have demonstrated the urinary excretion (0 to 8 h) of 1,3-dimethyluric acid and 1-methyluric acid following a dose of ^{14}C theophylline to account for 23 and 56 %, respectively, of the radioactivity excreted.

Morphine also undergoes *N*-demethylation in the rat with approximately 10 to 13 % of an administered dose being *N*-demethylated (6, 7). However, this minor metabolic pathway of morphine may be insufficient to explain the 55 % reduction in theophylline disposition observed with morphine co-administration, suggesting that morphine may be acting to limit theophylline elimination in another way. It is unlikely that any alterations in hepatic blood flow would play a predominant role in changing theophylline clearance. The magnitude of the systemic clearance of theophylline is low in comparison to estimates of hepatic plasma flow in the rat (0.31 vs. 2.2 $l \cdot h^{-1} kg^{-1}$) (8), resulting in an apparent hepatic extraction ratio (Cl/hepatic plasma flow) of 0.14. This inefficient extraction of theophylline from the systemic circulation by the liver implies that intrinsic hepatic enzyme activity, rather than hepatic perfusion, is the primary determinant of theophylline's metabolic clearance.

The effects of morphine on theophylline pharmacokinetics in the rat are consistent with the reductions in theophylline systemic clearance observed by Piafsky et al. (1) who examined theophylline pharmacokinetics in nine patients with acute cardiogenic pulmonary edema. While other factors such as hypoxia and hepatic congestion cannot be ruled out as causative factors affecting theophylline clearance in this patient population, five of the patients studied received concomitant morphine. Based on the results of the current study performed in rats, concomitant morphine administration may have been responsible for the reductions in theophylline clearance which occurred in these patients. The potential presence of a morphine-induced alteration in theophylline clearance in man would further suggest a mechanism alternative to competition for hepatic *N*-demethylation enzymes, since *N*-demethylation does not appear to be a major metabolic pathway for morphine in man (9). Further studies are warranted to determine whether this interaction exists in humans and to assess its clinical significance.

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